Dampening TLRs and TCRs

Many factors control cellular activation and homeostasis. In *Cell*, Sun *et al.* now find that tumor necrosis factor-α–induced protein 8 (TNFAIP8; also called TIPE2) negatively regulates the activation of Toll-like receptors (TLRs) and T cell antigen receptors (TCRs) to prevent severe inflammatory disease. TIPE2 contains a death effector domain–like domain and is expressed in lymphoid and inflamed tissues. TIPE2-deficient mice develop fatal inflammatory disease with severe mononuclear cell infiltration in many organs and augmented T cell responses to pathogens. Treatment of TIPE2-deficient macrophages with lipopolysaccharide induces more interleukin 6 (IL-6) and IL-12, and TIPE2-deficient mice are highly susceptible to lipopolysaccharide-induced septic shock. Activity of the kinases p38 and Jnk and transcription factor NF-κB is enhanced in TIPE2-deficient cells. TIPE2 immunoprecipitates together with caspase-8, a key regulator of both TLR and TCR pathways, and blocking caspase-8 activity abrogates the hyperreactivity of TIPE2-deficient cells. Thus, TIPE2 functions as a critical negative regulator of TCR and TLR signaling. ***DCB***
***Cell* 133, 415–456 (2008)**

New task for TRADD

The adaptors FADD and RIP1 interact with the adaptor MAVS and are required for NF-κB activation 'downstream' of the cytoplasmic viral sensors RIG-I and Mda5. In *Immunity*, Jürg Tschopp and colleagues show that the adaptor TRADD is required for recruitment of FADD and RIP1 to MAVS and for virus-induced production of type I interferon. TRADD interacts directly with MAVS, and TRADD overexpression activates, whereas TRADD deficiency impairs, interferon- and NF-κB-responsive promoter activity induced by MAVS and RIG-I. TRADD transmits interferon-inducing signals by forming a complex with the E3 ubiquitin ligase TRAF3, an established mediator of MAVS-induced interferon production, and with the adaptor TANK. TRADD-deficient mice show impaired interferon production after infection with vesicular stomatitis virus and develop higher viral titers. Thus, in addition to its function in tumor necrosis factor receptor signaling, TRADD is an important mediator of cytoplasmic virus sensor signals. *CB*
Immunity **28**, 651–661 (2008)

Right time, wrong place

Foxp3$^+$ regulatory T cells (T_{reg} cells) are necessary for inhibiting self-reactivity, but their function during infection is not clear. In *Science*, Rudensky and colleagues show that T_{reg} cells are essential for directing effector cell responses to the infected tissues. '*Foxp3*^{DTR}' mice, which lack T_{reg} cells because of acute ablation with diphtheria toxin, cannot control viral infection. Unexpectedly, the lack of T_{reg} cells leads to accumulation of effector cells draining lymph nodes, yet there is a paucity of effector cells in the local site of infection. Depletion of T_{reg} cells increases expression of proinflammatory chemokines by both lymph node stromal cells and dendritic cells, but expression of the phosphate receptor $S1P_1$ by effector T cells remains unaltered. This situation leads to a delay in trafficking of effector cells to the site of viral infection. Elucidation of how T_{reg} cells influence chemokine expression in the lymph node awaits future work. ***LAD***
***Science* 320, 1220–1224 (2008)**

Written by Christine Borowski, Douglas C. Braaten & Laurie A. Dempsey

Modulator of macrophage differentiation

Classically activated proinflammatory M1 macrophages release IL-12 and express inducible nitric oxide synthase, whereas tumor-associated anti-inflammatory macrophages produce IL-10. In the *Journal of Experimental Medicine*, teams led by Lawrence and Hagemann suggest that the kinase IKKβ acts as a molecular 'switch' controlling the differentiation of M1 versus tumor-associated macrophages. Mice lacking IKKβ in macrophages and neutrophils produce more IL-12, interferon-γ and inducible nitric oxide synthase but less IL-10 and more efficiently eliminate group B streptococcus than do their wild-type counterparts. Likewise, IKKβ-deficient macrophages show enhanced tumoricidal activity *in vivo*, and tumor-associated macrophages infected with an adenovirus expressing a dominant negative IKKβ construct 'switch' to an M1 phenotype and promote tumor eradication. IKKβ deficiency results in more phosphorylation of STAT1, a transducer of signals sent by interferon-γ, an established inducer of M1 macrophage differentiation. *CB*
J. Exp. Med. (19 May 2008) doi:10.1084/jem20080124 & doi:10.1084/jem20080108

c-Kit and dust mites

Exposure to house dust mites causes airway obstruction associated with skewed T helper cell type 2 (T_H2) cells and more IL-6, a factor required for development of both T_H2 cells and IL-17-producing T helper cells. In *Nature Medicine*, Krishnamoorthy *et al.* determine the signaling pathway in bone marrow–derived dendritic cells (BMDCs) that leads to IL-6 production. Exposure of normal cells to house dust mites causes much more cell surface expression of the cytokine receptor c-Kit and its ligand stem cell factor, leading to IL-6 production induced by the PI(3)K-Akt pathway 'downstream' of c-Kit. BMDCs expressing c-Kit skew T helper cells to produce copious IL-13 and IL-17, and mice deficient in c-Kit have many fewer IL-13– and IL-17–producing cells after allergen exposure or klebsiella infection. These data identify how allergens influence BMDCs to effect inflammatory T_H2–IL-6 responses. ***DCB***
***Nat. Med.* 14, 565–573 (2008)**

Skin function and B cells

Skin provides an essential barrier function that protects against opportunistic infection and dehydration. In *PLoS Biology*, Demehri *et al.* show that Notch signals are needed to maintain proper skin differentiation and barrier function. Loss of Notch or γ-secretase function in keratinocytes during fetal development leads not only to dysfunctional skin as a barrier but also to a profound B cell hyperplasia. Very young mutant mice succumb to this B cell lymphoproliferative disease as a result of multiorgan infiltration. The lack of skin barrier function results in upregulation of thymic stromal lymphopoietin (TSLP) by keratinocytes that then feeds back to fetal liver and bone marrow hematopoiesis, skewing development toward the B cell lineage. Notably, TSLP is not a direct target of the Notch pathway; instead, the lack of an intact skin layer results in more TSLP expression. These results point to complex regulatory interactions that occur among diverse tissues and might underlie some autoimmune diseases. *LAD*
PLoS Biol. (27 May 2008) doi:10.1371/journal.pbio.0060123